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OPTICAL RESOLUTION OF α-ISOPROPYL CHLOROPHENYL ACETIC ACID [ARUHUA-ISOPUROPIRU-P-KURORUHUENIRU SAKUSAN-NO KOGAKU BUNKATSUHO]

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TITLE (54): OPTICAL RESOLUTION OF α-ISOPROPYL CHLOROPHENYL ACETIC ACID

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Clean copy of specification (no changes made to contents)

Specification

Title of Invention

Optical Resolution of α-isopropyl Chlorophenyl Acetic Acid

Claim

(1)An optical resolution for α-isopropyl-p-chlorophenyl acetic acid using optically active α-phenyl-β-paratryl ethyl amine or optically active α-phenyl ethyl amine, the invention characterized as an optical resolution for α-isopropyl-p-chlorophenyl wherein an optically active α-isopropyl-p-chlorophenyl acetic acid is obtained by reacting an optically active α-phenyl-β-paratryl ethyl amine or an optically active α-phenyl ethyl amine in a mixed solvent made up of a hydrophobic organic solvent and a hydrophilic organic solvent and / or water as a solvent, selectively crystallizing the salt of the optically active α-isopropyl-p-chlorophenyl acetic acid, separating the crystals of said salt from the mother liquor, refining the crystals of said salt in a mixed solvent made up of a hydrophobic organic solvent and a hydrophilic organic solvent and / or water, or not carrying this out and decomposing said salt if necessary;

(2) An optical resolution as described in Claim 1 characterized as adding a process for refining;

(3) An optical resolution as described in Claim 1 or Claim 2 wherein the solvent is a mixed solvent made up of a hydrophobic organic solvent, a hydrophilic organic solvent and water;

(4) An optical resolution as described in Claim 1, Claim 2 or Claim 3 wherein the hydrophobic organic solvent used is one, two or more types selected from an aromatic hydrocarbon, an aliphatic hydrocarbon, an alicyclic hydrocarbon and a halogenated hydrocarbon;

(5) An optical resolution as described in Claim 1, Claim 2 or Claim 3 wherein the hydrophilic organic solvent is one, two or more types selected from lower alcohols and lower order aliphatic ketones;

(6) An optical resolution as described in Claim 1, Claim 2, Claim 3, Claim 4 or Claim 5 wherein the solvent is a mixed

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solvent made up of an aromatic hydrocarbon used as the hydrophobic organic solvent and a lower alcohol used as the hydrophilic organic solvent and / or water;

(7) An optical resolution as described in Claim 1, Claim 2, Claim 3, Claim 4, Claim 5 or Claim 6 wherein 0.5 to 1.0 mol of an optically active α-phenyl-β-paratryl ethyl amine or

an optically active α-phenyl ethyl amine is reacted with 1 mol of α-isopropyl-p-chlorophenyl acetic acid;

(8) An optical resolution as described in Claim 1, Claim 2, Claim 3, Claim 4, Claim 5, Claim 6 or Claim 7 wherein an optically active α-phenyl-β-paratryl ethyl amine is used;

(9) An optical resolution as described in Claim 1, Claim 2, Claim 3, Claim 4, Claim 5, Claim 6, Claim 7 or Claim 8 wherein α-isopropyl-p-chlorophenyl acetic acid and an optically active α-phenyl-β-paratryl ethyl amine or an optically active α-phenyl ethyl amine are reacted at a temperature of 40 to 150°C;

(10) An optical resolution as described in Claim 1, Claim 2, Claim 3, Claim 4, Claim 5, Claim 6, Claim 7, Claim 8 or Claim 9 wherein α-isopropyl-p-chlorophenyl acetic acid and an optically active α-phenyl-β-paratryl ethyl amine or an optically active α-phenyl ethyl amine are reacted and the reaction solution is then heated to a temperature of 40 to 150°C;

(11) An optical resolution as described in Claim 1, Claim 2, Claim 3, Claim 4, Claim 5, Claim 6, Claim 7, Claim 8, Claim 9 or Claim 10 wherein an optically active α-phenyl-β-paratryl ethyl amine salt or an optically active α-phenyl ethyl amine salt of optically active α-isopropyl-p-

chlorophenyl acetic acid is refined at a temperature of 40 to 150°C.

3. Detailed Description of Invention

The present invention relates to an optical resolution for α-isopropyl-p-chlorophenyl acetic acid (hereinafter abbreviated to "ICPA"). It relates more particularly to an optical resolution for ICPA which uses an optically active α-phenyl-β-paratryl ethyl amine (hereinafter abbreviated to "PTE") or an optically active α-phenyl ethyl amine (hereinafter abbreviated to "PEA") in a mixed solvent made up of a hydrophobic organic solvent and a hydrophilic organic solvent and / or water.

In prior-art pyrethroid group insecticides, a group of α-substituted phenyl acetic acid esters having large different structures are known to have a strong insecticidal effect on a variety of insects (Laid-Open Patent Specification 49-26425; Laid-Open Patent Specification 49-1268326) and ICPA esters are known to be particularly outstanding due to their effectiveness and cost-effectiveness.

In addition, regarding the insecticidal effectiveness of (+)-body and (-)-body carboxylic acid esters obtained by optical resolution of α-substituted phenyl acetic acid which is a constituent component of the above, esters of (-) body carboxylic acid are virtually ineffective whereas (+)-body esters have been found to exhibit approximately twice the insecticidal effectiveness of (±)-bodies.

Thus far, optical resolution using optically active PTE or optically active PEA has been known as an ICPA optical resolution (Laid-Open Patent Specification 50-25544). However, this method was unsatisfactory on a number of points as (1) it requires recrystallization operations for large amounts of solvent used a number of times in order to obtain (+) ICPA with a high degree of optical purity; (2) when (+) PTE with a low degree of optical purity is used, the filtering characteristics for the salt crystallization deteriorate to an extreme and it is difficult to obtain (+) ICPA with a high degree of optical purity so that (+) PTE with a high degree of optical purity must be used to obtain (+) ICPA with a high degree of optical purity.

After a great deal of hard work and study, the inventors found that by using a mixed solvent made up of a hydrophobic organic solvent and a hydrophilic organic solvent and / or water in a method for optical resolution of ICPA using optically active PTE or optically active PEA, the optical purity of the (+) ICPA obtained could be greatly improved and that the amount of solvent used could be greatly reduced. They also found that (+) ICPA with a high degree of optical purity could be obtained without the

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filtering characteristics of the salt crystals deteriorating even if (+) PTE with a low degree of optical purity was used.

In addition, a secondary effect of the present invention is the method described in Laid-Open Patent Specification 50-5850 and in Laid-Open Patent Specification 58-25535. It is advantageous in that when the ICPA raw material is being manufactured and refined, a connection can be made to the resolution process using the method in the present invention with the solution of the hydrophobic organic solvent as is. This means that there is a well known method used to synthesize the ICPA such as the method described in Laid-Open Patent Specification 50-5850 which

involves hydrolysis of a-isopropyl-p-chlorophenyl acetonitrile. In addition, Laid-Open Patent Specification 53-25535 describes a method used to refine said ICPA using benzene, toluene, xylene, chlorobenzene, hexane, heptane and other aliphatic or aromatic organic solvents.

Meanwhile, water-containing alcohol is a well-known suitable solvent which has been used thus far for optical resolution of ICPA (Laid-Open Patent Specification 50-25544). In order to resolve the ICPA obtained using the abovementioned manufacturing and refining method, the ICPA had to be separated once as the solvent was different. However, when the present invention is used, a connection can be made to the optical resolution with the solution of the aliphatic or aromatic organic solvent for the ICPA used in the abovementioned refining method as is.

As indicated previously, the present invention not only has a variety of industrial advantages but is also an optical resolution method for ICPA which makes it possible to efficiently obtain (+)ICPA having a high optical purity.

The hydrophobic organic solvent used in the present invention may be benzene, toluene, xylene and other aromatic hydrocarbons, hexane, heptane, octane and other aliphatic hydrocarbons, cyclohexane, methyl cyclohexane and other alicyclic hydrocarbons, chloroform, carbon

tetrachloride, chlorobenzene and other halogenated hydrocarbons and the like.

In addition, the hydrophilic organic solvent may be methyl alcohol, ethyl alcohol, n-propyl alcohol, iso-propyl alcohol, n-butyl alcohol, iso-butyl alcohol, sec-butyl alcohol, tert-butyl alcohol and other lower alcohols, acetone, methyl ethyl ketones and other lower order aliphatic ketones. Suitable hydrophobic organic solvents should be a mixed solvent made up of aromatic hydrocarbons as the hydrophobic organic solvent and lower alcohols and / or water as the hydrophilic organic solvent.

In addition, the amount of (+) PTE or (-) PEA used should be within the range of 0.5 to 1.0 mol and preferably within the range of 0.6 to 0.8 mol relative to 1 (+) ICPA mol and PTE is a more suitable choice due to the optical purity of the (+) ICPA obtained.

There are no particular restrictions on the reaction time as long as it is 30 minutes or longer. In addition, the amount of solvent used should be 1 to 10 times (the weight of) the raw material ICPA. Even when refining is required, the refining should be carried out in a solvent which is 1 to 10 times the amount (weight) of the salt.

The actual optical resolution may be carried out as follows. The (+) ICPA is reacted with (+) PTE or (-) PEA in the abovementioned mixed solvent. Any temperature is suitable at this time, however, during the reaction or following it, it should be heated at 40 to 150°C and kept at that temperature to further increase the optical purity of the (+) ICPA. Needless to say, the reaction between the ICPA and the (+) PTE or (-) PEA itself need not necessarily be carried out in the abovementioned mixed solvent. In this case, processing should be carried out in the abovementioned mixed solvent after the reaction. When this is heated and maintained at 40 to 150°C, the salt by no means needs to be completely dissolved. After heating is carried out and the temperature is maintained at that temperature, the crystal of the salt of the (+) ICPA obtained after cooling should be separated from the mother liquor. Needless to say at this time, the ICPA in the mother liquor is a (-)-body. The separation temperature should be 0 to 60°C and preferably 10 to 30°C. Next, further refining of the abovementioned salt crystal is carried out as needed in the mixed solvent made up of the hydrophobic organic solvent and the hydrophilic organic solvent and / or water. Refining should be carried out by heating at 40 to 150°C and maintaining that temperature in

the abovementioned mixed solvent. Thereafter, it should be cooled to 0 to 60°C and the crystal should be separated. Even when this heating temperature is maintained, the salt crystal need not necessarily be completely dissolved.

Even during these refining operations, the abovementioned mixed solvent which constitutes the present invention is used so that an optically active ICPA salt with extremely high optical purity can be obtained when a smaller amount of the solvent is used.

Furthermore, the optically active ICPA salt can be connected as is to the ICPA ester manufacturing process. However, after the salt is made an optically active ICPA or an alkali salt thereof using the regular method which uses hydrochloric acid, sulfuric acid and other acids or sodium hydroxide, potassium hydroxide and other alkalis, it should be introduced to the ICPA esters.

Next, we shall describe the present invention in further detail by providing practical examples and reference examples of it. Needless to say, it should by no means be construed that the present invention is restricted to these examples.

Practical Example 1

We stirred and dissolved 21.27 g of (±) ICPA in a mixed solvent made up of 21.27 g of toluene, 17.02 g of methyl alcohol and 4.25 g of water. Next, we added 13.73 g of (+) PTE at 25°C, raised the temperature to 70°C and maintained the temperature for 2 hours at that temperature. Then, we cooled it to 20°C for 2 hours and filtered the crystal. Next, we washed the crystal in a suitable amount of an 80 % methyl alcohol aqueous solution and obtained 14.92 g of a (+) ICPA- (+) PTE salt in the form of colorless needles. We decomposed this salt in a 5 % sodium hydroxide aqueous solution and extracted the (+) PTE with toluene. Then, we carried out acid separation of the water layer using a 10 % hydrochloric acid aqueous solution and we obtained 7.49 g of (+) ICPA.

Yield 35.2 % (relative to raw material (±) ICPA)

$[\alpha]^{23}_{D}$ +45.02° ($CHCl_2$, C = 6)

Optical purity 93.2 %

Practical Example 2

We stirred and dissolved 21.27 g of (±) ICPA in a mixed solvent made up of 21.27 g of benzene, 17.02 g of ethyl alcohol and 4.25 g of water. Next, we added 16.90 g of (+) PTE at 40°C and raised the temperature to 67°C. From this point on, we carried out the same operations as in Practical Example 1 and obtained 18.61 g of a (+) ICPA -

(+) PTE salt. We decomposed this salt using the same method as in Practical Example 1 and obtained 9.34 g of (+) ICPA.

Yield: 43.9 % (relative to raw material (±) ICPA)

$[\alpha]^{23}_{D}$ +44.63° ($CHCl_2$, C = 6)

Optical purity 92.4 %

Practical Example 3

We added 15.00 g of toluene, 12.00 g of ethyl alcohol and 3.00 g of water to 15.00 g of the (+) ICPA - (+) PTE salt obtained using the same method as in Practical Example 2 and stirred it. Next, we raised the temperature to 76°C and maintained the same temperature for 3 hours. Then, we cooled it to 20°C for 2 hours and filtered out the crystal. We washed the crystal using a suitable amount of an 80 % ethyl alcohol aqueous solution and obtained 13.52 g of a (+) ICPA - (+) PTE salt in the form of colorless needles. We carried out acid decomposition of this salt using the same method as in Practical Example 1 and obtained 6.73 g of (+) ICPA.

Yield 90.1 % (relative to salt sourced)

$[\alpha]^{23}_{D}$ +47.91° ($CHCl_2$, C = 6)

Optical purity 99.2 %

Practical Example 4

We stirred and dissolved 21.27 g of (±) ICPA in a mixed solvent made up of 21.27 g of toluene, 17.02 g of

methyl alcohol and 4.25 g of water. Next, we added 7.27 g of (-) PEA at 25°C, raised the temperature to 70°C and maintained it at the same temperature for 2 hours. Then, we cooled it to 20°C for 2 hours and filtered out the crystal. Next, we washed the crystal using a suitable amount of an 80 % methyl alcohol aqueous solution and obtained 15.12 g of a (+)ICPA -(-) PEA salt in the form of colorless needles. We further refined this once in 30.24 g of a mixed solvent having the same composition and obtained 18.94 g of a (+) ICPA- (-) PEA salt. We carried out acid decomposition on this salt using the same method as in Practical Example 1 and obtained 8.88 g of (+) ICPA.

Yield 41.7 % (relative to raw material (±) ICPA)

$[\alpha]^{23}_{D}$ + 45.93° ($CHCl_2$, C = 6)

Optical purity 95.1 %

Practical Example 5

We stirred and dissolved 15.00 g of (±) ICPA in a mixed solvent made up of 15.00 g of toluene, 6.00 g of

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ethyl alcohol, 6.00 g of isopropyl alcohol and 3.00 g of water. Next, we added 9.69 g of (+) PTE at 45°C and raised the temperature to 78°C. From this point onward we carried out the same operations as in Practical Example 1 and obtained 14.92 g of a (+) ICPA - (-) PTE salt in the form

of colorless needles. Next, we subjected this salt to acid decomposition using the same method as in Practical Example 1 and obtained 5.97 g of (+) ICPA.

Yield 39.8 % (relative to raw material (±) ICPA)

$[\alpha]^{23}_{D}$ +45.89° ($CHCl_2$, C = 6)

Optical purity 95.0 %

Practical Example 6

We stirred and dissolved 21.27 g of (±) ICPA in a mixed solvent made up of 14.89 g of toluene, 6.88 g of n-heptane, 17.02 g of methyl alcohol and 4.25 g of water. Next, we added 18.78 g of (+) PTE at 69°C and maintained this temperature for 2 hours. From this point onward, we carried out the same operations as in Practical Example 1 and obtained 15.48 g of a (+) ICPA - (+) PTE salt in the form of colorless needles. Next, we carried out acid decomposition on this salt using the same method as in Practical Example 1 and obtained 7.77 g of (+) ICPA.

Yield 36.5 % (relative to raw material (±) ICPA)

$[\alpha]^{23}_{D}$ + 45.11° ($CHCl_2$, C = 6)

Optical purity 93.4 %

Practical Example 7

We added and stirred a mixed solvent made up of 15.00 g of toluene, 12.00 g of methyl alcohol and 3.00 g of water to 15.00 g of the (+) ICPA - (+) PTE salt obtained using

the same method as in Reference Example 1 (to follow) to carry out optical resolution using only the toluene and we raised the temperature to 70°C. From this point onward, we carried out the same operations as in Practical Example 3 and obtained 12.80 g of a (+) ICPA - (+) PTE salt in the form of colorless needles. We carried out acid decomposition on this salt using the same method as in Practical Example 1 and obtained 6.42 g of (+) ICPA.

Yield 85.3 % (relative to salt sourced)

$[\alpha]^{23}_{D}$ +47.91° ($CHCl_2$, C = 6)

Optical purity 99.2 %

Reference Example 1

We stirred and dissolved 21.27 g of (±) ICPA in 42.54 g of toluene. Next, we added 13.73 g of (+) PTE at 25°C, raised the temperature to 110°C and maintained the same temperature for 2 hours. Then, we cooled this to 20°C for 2 hours and filtered out the crystals. Next, we washed the crystals in a suitable amount of toluene and obtained 17.72 g of a (+) ICPA - (+) PTE salt in the form of colorless needles. We carried out acid decomposition on this salt using the same method as in Practical Example 1 and obtained 8.89 g of (+) ICPA.

Yield 41.8 % (relative to raw material (±) ICPA)

$[\alpha]^{23}_{D}$ + 40.19° ($CHCl_2$, C = 6)

Optical purity 83.2 %

Reference Example 2

We stirred and dissolved 21.27 g of (±) ICPA in 267.15 g of an 80 % methyl alcohol aqueous solution. Next, we added 21.13 g of (+) PTE at 25°C. We raised the temperature to 72°C and maintained that temperature for 2 hours. Then, we cooled it to 20°C for 2 hours and filtered out the crystals. Next, we washed the crystals in a suitable amount of an 80 % methyl alcohol aqueous solution and obtained 15.22 g of a (+) ICPA - (+) PTE salt in the form of colorless needles. We carried out acid decomposition of this salt using the same method as in Practical Example 1 and obtained 7.64 g of (+) ICPA.

Yield 35.9 % (relative to raw material (±) ICPA)

$[\alpha]^{23}_{D}$ +41.64° ($CHCl_2$, C = 6)

Optical purity 86.0 %

Reference Example 3

We stirred and dissolved 21.27 g of (±) ICPA in 599.81 g of an 80 % ethyl alcohol aqueous solution. Next, we added 12.12 g of (-) PEA at 25°C and raised the temperature to 79°C. From this point onward, we carried out the same operations as in Reference Example 2 and obtained 14.36 g of a (+) ICPA - (-) PEA salt in the form of colorless

needles. We carried out acid decomposition on this salt and obtained 9.15 g of (+) ICPA.

Yield 43.0 % (relative to raw material (±) ICPA)

$[\alpha]^{23}_{D}$ +41.50°C ($CHCl_2$, C = 6)

Optical purity 85.9 %

Reference Example 4

We added 30.00 g of an 80 % methyl alcohol aqueous solution to 15.00 g of the (+) ICPA - (+) PTE salt obtained using the same method as in Reference Example 2 and stirred it. We raised the temperature to 72°C and maintained that temperature for 3 hours. Then, we cooled it to 20°C for 2 hours and filtered out the crystals. Next, we washed the

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crystals using a suitable amount of an 80 % methyl alcohol aqueous solution and obtained 13.68 g of a (+) ICPA- (+) PTE salt in the form of colorless needles. We carried out acid decomposition on this salt using the same method as in Practical Example 1 and obtained 6.86 g of (+) ICPA.

Yield 91.2 % (relative to salt sourced)

$[\alpha]^{23}_{D}$ +44.05° ($CHCl_2$, C = 6)

Optical purity 91.2 %

Reference Example 5

We added 30.00 g of an 80 % ethyl alcohol aqueous solution to 15.00 g of the (+) ICPA- (-) PEA salt obtained

using the same method as in Reference Example 3, stirred it and raised the temperature to 79°C. From this point onward, we carried out the same operations as in Reference Example 4 and obtained 13.88 g of a (+) ICPA - (-) PEA salt in the form of colorless needles. We carried out acid decomposition on this salt using the same method as in Practical Example 1 and obtained 8.84 g of (+) ICPA.

Yield 92.5 % (relative to the salt sourced)

$[\alpha]^{23}_{D}$ +43.13° ($CHCl_2$, C = 6)

Optical purity 89.3 %

Amendment of the Proceedings (voluntary)

[illegible] 25, 1979

To: Director General of the Patent Office

Zenji Kumagai

1.Details of the Case

54-43414

2. Title of Invention

Optical Resolution of α-isopropyl Chlorophenyl Acetic Acid

3. Entity Carrying Out Amendment

Relation to the Case: Patent Applicant

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5. Subject of Amendment

Entire Specification

6. Details of Amendment [SEAL][Patent Office / May 28, 1979/ Filing, Second Section]

Clean copy of Specification (no changes made to it)